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TITLE: Columbia SMA Project: A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)

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14. ABSTRACT

This three-year randomized controlled trial is designed to assess the effectiveness of a comprehensive regimen incorporating strengthening and aerobic exercise in 14 ambulatory patients with spinal muscular atrophy (SMA). To date, 13 subjects have been screened and 5 subjects enrolled. Reasons for non-participation were most often cost and burden of travel. Protocol adherence has been outstanding thus far with only one deviation with regards to visit schedule. All testing and intervention procedures have been well tolerated without any serious adverse events. All non-serious adverse events are closely monitored by an independent safety monitor who has approved continuation of the study without modification thus far. The overall goal of this project is to provide novel insights into the effectiveness of aerobic and strengthening exercise to improve function in SMA, and explore the physiology underlying its effects.

15. SUBJECT TERMS

Spinal Muscular Atrophy, Exercise, Ambulatory, Clinical Trial

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INTRODUCTION: This three-year randomized controlled trial is designed to assess the effectiveness of a comprehensive regimen incorporating strengthening and aerobic exercise in 14 ambulatory patients with spinal muscular atrophy (SMA). SMA causes significant disability, and there is no effective drug treatment. Maximizing function, endurance, general health and well being, in an effort to modulate disease morbidity is the focus of supportive treatment modalities. There are no controlled data evaluating the role of exercise in SMA. Several controlled animal studies provide compelling evidence for benefit from exercise. The overall goal of this project is to provide novel insights into the effectiveness of aerobic and strengthening exercise to improve function in SMA, and explore the physiology underlying its effects. Moreover, by studying the effects of exercise in human patients, we hope to provide the first application of these studies for improved standard of care.

BODY: The first year of this project consisted of mainly start-up and administrative procedures. For administrative and IRB reasons our proposed timeline was delayed nearly 2 months. Definitive IRB approvals were obtained from both Columbia University and the USAMRMC ORP HRPO and the first subject was enrolled on December 17, 2010. To date, 13 subjects have been screened, 5 subjects enrolled, and an additional subject is scheduled for a baseline visit on June 16, 2011. Reasons for non-participation were most often cost and burden of travel. All 13 subjects met minimal eligibility for participation. Below is a summary of the progress thus far outlined by the specific aims of the project.

Aim 1: To assess the effect of comprehensive strengthening and aerobic exercise on clinical measures of function in patients with SMA.

Hypothesis 1: A comprehensive strengthening and aerobic exercise regimen will improve performance by ambulatory subjects with SMA on measures of clinical function, including the six-minute walk test (6MWT), Hammersmith motor function scale, expanded (HMFSE), 10 meter walk/run test and kinematic parameters of gait.

Significance: There are at present no studies that detail the effectiveness of exercise in modulating clinical function in SMA. Demonstration of such benefit is expected to have immediate impact on the management of the disease.

The 5 subjects enrolled thus far are actively continuing with their study participation and have been randomized following their baseline visit as per protocol. Three subjects were randomized to the control group and 2 to the intervention arm of the study. All 5 have completed their baseline and month 1 visits, and 2 subjects have completed their month 4 visit. The baseline characteristics are outlined in Table 1 below.

Table 1. Baseline characteristics of study subjects.

Variable	Mean (SD)	Range
Age (years)	25.9 (15.4)	10.0 – 43.6
Age at symptom onset (years)	8.1 (4.8)	2.0 – 13.5
Gender (% male)	100%	
Six Minute Walk Test (6MWT) Distance (meters)	366.4 (103.3)	250 – 498
Hammersmith Functional Motor Scale, Expanded (HFMSE)	54.4 (7.4)	46 – 63
10 meter walk/run (seconds)	7.59 (3.16)	5.2 – 11.89
Timed Up and Go Test (TUG) (seconds)	18.12 (14.88)	5.27 – 41.11
Forced Vital Capacity (FVC) (% predicted)	107.2 (9.3)	100 – 123

Adherence to the protocol has been excellent to date. There has been only one protocol deviation where the Month 1 visit for subject 005 was performed 3 days out of window due to scheduling conflicts. The 5 enrolled subjects have completed all assessments and outcome measures at each visit as described in the protocol in the order described in the protocol and outlined in the visit checklists in Table 2 below. There are no missed outcome measures or deviations from this in-clinic visit protocol.

Table 2. Visit schedule

Baseline Visit (Month 0)
1. Assessment of Eligibility
2. Signed Consent
3. Randomization
4. Medical History
5a. Physical Exam
5b. Urine Pregnancy Test (if applicable)
6. 10 meter walk/run test
7a. 6 minute walk test (6MWT)
7b. GAIT Rite analysis
8. Timed Up and Go Test (TUG)
10 Minute Rest Break
9. HFMSE
10 Minute Rest Break
10. Manual Muscle Testing (MMT)
11. Hand Held Dynamometry (HHD)
12. FVC
10 Minute Rest Break
13. PedsQL NM module / SF-36
14. Peds QL Fatigue Scale / FSS
15a. Accelerometer Diary Instructions
15b. Accelerometer Diary
16. Exercise Capacity Test

Follow Visits (Months 1, 4, 7, 10, 13, and 19)
1. Medical History
2. Adverse Event Assessment
3a. Physical Exam
3b. Urine Pregnancy Test (if applicable)
4. 10 meter walk/run test
5a. 6 minute walk test (6MWT)
5b. GAIT Rite analysis
6. Timed Up and Go Test (TUG)
10 Minute Rest Break
7. HFMSE
10 Minute Rest Break
8. Manual Muscle Testing (MMT)
9. Hand Held Dynamometry (HHD)
10. FVC
10 Minute Rest Break
11. PedsQL NM module / SF-36
12. PEDSQL Fatigue Scale / FSS
13a. Exercise Recording
13b. Assessment of Exercise Compliance
14. Administration of Exercise Protocol
15a. Accelerometer Diary Instructions
15b. Accelerometer Diary
16. Exercise Capacity Test

For the 2 subjects enrolled in the intervention arm of the study, individualized exercise programs have been developed which include both the aerobic or cycling component and the strengthening component. As outline in the protocol, the initial design of the exercise regimen is structured based on performance on the exercise tolerance test as well strength assessments collected by the blinded evaluator. As anticipated, neither subject was able to cycle continuously for 30 minutes at study start so their program was tailored and adjusted according to their ability. Subject 001 has completed more than 3 months of exercise and has progressed from tolerating only 2 minutes of cycling to 10 continuous minutes 5 days a week. Subject 005 began his exercise program on 5/4/2011 with 10 minutes of cycling made up of 2 – 3 discontinuous bouts with 30 – 60 second rest intervals. Similarly, individualized strengthening programs have been developed for both subjects that include 5 – 6 large muscle groups based on their muscle strength assessments and ability.

As planned, video-conferencing visits using Skype have been implemented to ensure the subjects are performing the exercise correctly, change or advance their program, and to enhance exercise safety and adherence. During these visits, interim medical histories, concomitant medications and adverse events are also collected. Subjects enrolled in the control arm of the study also participate in the video-conferencing visits on a similar schedule.

Study participation has been safe and well tolerated thus far. Adverse events reported have been mild or moderate using the CTCAE Adverse Event Classification System and there have been no serious adverse events. Falls are a clinically important problem in people with weakness (Rubenstein LZ 2002) and neuromuscular disease (Pieterse AJ, 2006) and are the most commonly reported adverse event in this study thus far with 22 reports of falls in 5 subjects over 18 total months of study participation. Muscle soreness and fatigue were also reported but much less frequently in both control and exercise subjects. Monthly reports have been reviewed by Dr. Nancy Strauss, our independent un-blinded safety monitor, who has approved continuing this study without modification (see attached Appendix 1).

Aim 2: To explore the effect of a sustained exercise regimen on exercise capacity in patients with SMA.

Hypothesis 2: A comprehensive, intensive and sustained strengthening and aerobic exercise regimen will improve exercise capacity as measured by maximum oxygen uptake (VO_2 max), as well as maximal work capacity (Wmax) in patients with SMA

Significance: There is no literature addressing the role of a comprehensive exercise program on exercise capacity, or the relationship of exercise capacity with established clinical measures, in SMA.

Because maximal exercise testing including measurement of maximal oxygen uptake and work has not been administered previously to persons with SMA, the feasibility was not fully known at the start of the study. To date all of the subjects who volunteered to participate in the study have successfully performed one or more maximal exercise tests without adverse sequellae. Performance at baseline for all subjects is described in this report.

Exercise tolerance is determined by the functioning of multiple body systems including the cardiovascular, respiratory, and neuromuscular systems. A limitation in one or more body systems will result in reduced exercise capacity or tolerance. The variables demonstrating exercise tolerance, and hence the feasibility of the test include the respiratory exchange ratio (RER), ratings of perceived exertion (RPE), maximal oxygen uptake (VO2max), maximal heart rate (HRmax), and the reason for test termination. The RER represents the ratio of carbon dioxide produced to the oxygen uptake, and is an indicator of the adequacy of individual efforts to attain their maximal capacity. An RER greater than 1 is a standard criterion used to indicate the attainment of maximal tolerance (capacity). In healthy persons, the cardiorespiratory system is the limiting factor for exercise and an RER >1 will occur once the capacity of the cardiorespiratory system has been reached. Individuals who have significant respiratory, neuromuscular, or orthopedic limitations would not be expected to attain an RER > 1, because these would reach their

maximal capacity earlier due to the limitations imposed by these systems or physical limitations. Another criterion for maximal exercise tolerance is voluntary fatigue, which is usually defined as an RPE greater than 8 out of 10 points (hard to extremely hard) on the OMNI Scale, a 10 point scale indicating '1' as extremely easy to '10' as extremely hard. The results of the exercise tests are shown in table 3 below.

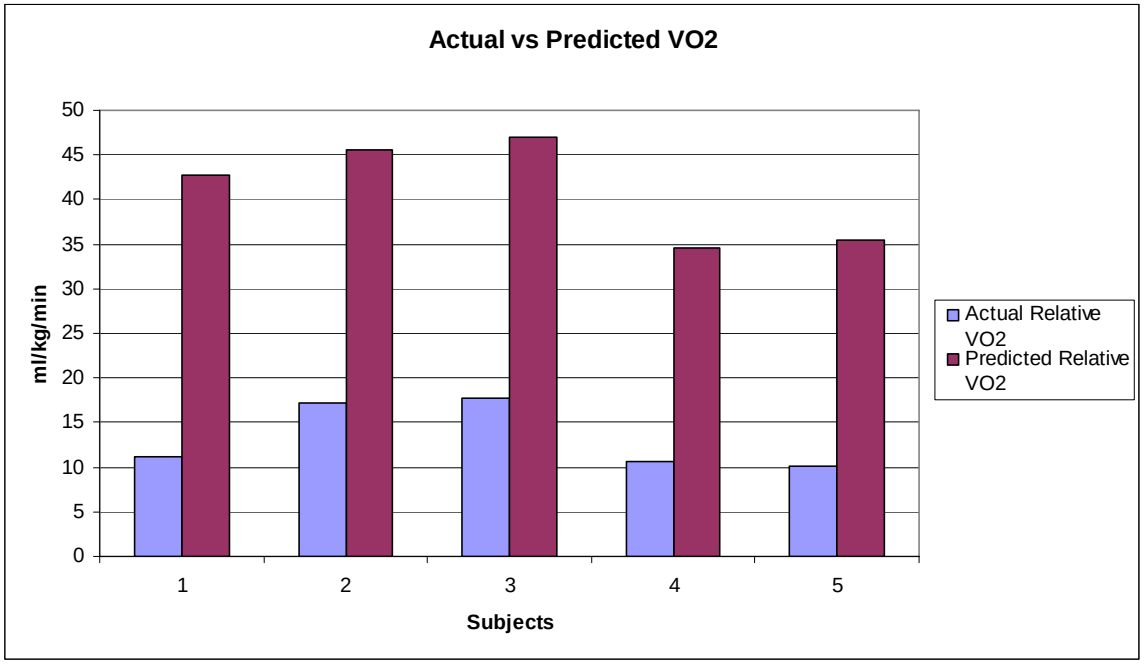
Table 3. Exercise Tolerance Test Baseline Results

Subjects Variables	001	002	003	004	005
RER	1.37	1.08	0.88	0.85	1.05
Max RPE	9	10	9	8	10
Reason for Termination	RPE 9 RER ≥1, Fatigue	RER >1, RPE 10	Pt request, knee pain	Fatigue and subject could not maintain pedal speed.	Fatigue, RPE >9, , RER≥1

All of the subjects reached RPE's of 8 -10, indicating they were working hard to extremely hard at the end of exercise. Tests were terminated due to fatigue in all but one subject, who stopped due to knee pain, related to internal rotation of the lower extremities and inherent muscle weakness associated with SMA. Further supporting the attainment of maximal exercise tolerance or capacity, 3 of the 5 subjects reached RER greater than 1, indicating that these subject's neuromuscular disease did not exert a substantial limitation upon their exercise capacity. In the case of the remaining two subjects who did not attain an RER of 1, one stopped due to knee pain and the other due to lower extremity fatigue., Fatigue is a normal response to maximal exercise test, and normal fatigue resolves within a few minutes of ceasing exercise, although some fatigue often persists throughout the day, but does not interfere with usual daily activities. With rest all of the subjects were able to walk to their cars following the test, and none reported inability to engage in their activities of daily living. It should be noted, however that the exercise tolerance test was administered following many tests performed throughout the study visit, so it is difficult to fully distinguish the contributory factors to the fatigue.

In evaluating the maximal exercise tolerance of our subjects, we compared their measured VO2mas to the predicted values for healthy individuals of the same sex and age. Figure 1 below shows the subjects' actual VO2 max and predicted VO2max, presented relative to body mass (mL/kg/min) to standardize for body size effects on oxygen uptake (i.e., larger individuals will have higher absolute oxygen uptake than smaller individuals). As can be seen in the graph, the subjects' actual VO2max is substantially lower than predicted, and likely reflects the effects of deconditioning resulting from limited engagement in physical activity secondary to physical function limitations associated with SMA. This is supported by data in other neuromuscular diseases such as Parkinson's Disease and Multiple Sclerosis which have shown concurrently decreased VO2max and low levels of physical activity (Mostert & Kesselring, 2002; Garber et al, 2003).

Figure 1. Actual versus Predicted Relative VO2 at baseline.



Aim 3: To assess the effect of comprehensive strengthening and aerobic exercise on muscle strength measures in patients with SMA.

Hypothesis 1: A comprehensive strengthening and aerobic exercise regimen will improve measures of muscle strength using manual muscle testing (MMT) augmented by hand-held dynamometry (HHD).

Significance: There is at this time little evidence describing the effect of exercise on muscle strength in SMA, and the relationship between such effect and measures of clinical function. Demonstration of such benefit is expected to have immediate impact on the management of the disease.

Manual muscle testing (MMT) is performed as part of a routine neurological exam. Manual muscle testing (MMT) was found to be feasible in children with SMA and was sensitive enough to detect relative differences between different muscles (Carter 1995, Deymeer 1997, Wang HY 2002).

Below are the baseline MMT scores for each subject by muscle group (Table 4). The muscle weakness in SMA is thought to be largely symmetrical with rarely one side more affected (Deymeer 1997, 2008) and is apparent in the subjects reported in this study to date.

Table 4. Manual Muscle Test (MMT) baseline scores by subject using the Medical Research Council (MRC) grading scale.

Subjects	001		002		003		004		005	
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
Shoulder Abduction	4-	4-	4+	4+	4+	4+	3+	3+	4+	4-
Elbow Flexion	5-	5	4+	4+	5-	5-	3+	3+	4-	4-
Wrist Extension	5	5	4+	5-	5	5	4-	4-	5	5
Wrist Flexion	4	4	5	5	5	5	4-	4-	5-	5
Hip Flexion	2	2	4-	4-	2	3+	2	2	2	2
Ankle Dorsiflexion	5	5	5-	5-	5-	5-	4+	4+	5	5
Knee Extension	3-	3-	4-	4	3+	4-	3-	3-	4	3-
Elbow Extension	3+	3-	3+	3+	4	4	3+	3+	3+	4-
Hip Abduction	3-	3-	3+	3+	3-	3+	3-	3-	4+	3-
Hip Adduction	2	2	2	3-	2	2	2	2	2	2
Shoulder External Rotation	4-	4-	3+	3+	4-	4-	4-	4-	4-	4
Hip Extension	2	2	3	3-	3+	3-	2	2	3-	2
Knee Flexion	4+	4+	4-	3	4-	4-	2	2	4	5-
Ankle Plantarflexion	5	5	5	5	5	5	4-	4-	5	5

Research has shown MMT lacks sensitivity in detecting weakness, particularly in less affected or muscles with strength in normal ranges (Bohannon 2005). As such, the addition of hand-held dynamometry (HHD) has been shown to increase the sensitivity of MMT in SMA children aged 5 years or older with good inter-rater reliability and reproducibility for some leg muscle groups (Merlini 2002). Of the leg muscles tested only knee extensors and flexors performed reliably. Using HHD, knee extensors in SMA patients were weaker than flexors which in contrast to stronger knee extensors in the healthy population (Beenakker E 2001) and of those, only strength of the knee extensors not flexors were predictive of walking ability (Ferber 2010).

Below are the baseline HHD scores for each subject by muscle group. Similar to the results above, muscle strength in this cohort is largely symmetrical except in a few muscle groups tested perhaps as a result of the increased sensitivity provided by this more quantitative method. Together MMT, augmented by HHD, will provide a comprehensive evaluation of the participant's muscle strength and responsiveness to the exercise intervention. With this prospective detailed examination, the relationship of muscle strength to walking performance and responsiveness to exercise treatment can be explored.

Table 5. Hand Held Dynamometry (HHD) baseline scores in pounds (lbs.) by subject

Subject	001		002		003		004		005	
Muscle Group	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
Shoulder Abduction	5.2	6.5	13.2	15.2	12.2	12.8	9.8	4.6	6.7	10.9
Knee Flexion	18.2	16.3	14.3	12.9	14.8	14.9	1.5	3.3	15.6	13.2
Knee Extension	4.6	2.6	10.2	17.5	3.9	5.5	2.6	2.1	9.3	2.7
Elbow Flexion	34.1	30.8	32	24.9	25.3	20.6	14.3	11.3	13.7	15.3
Elbow Extension	4.3	5.6	7.9	9.6	12.8	15.3	4.9	5.5	2.3	4.3

KEY RESEARCH ACCOMPLISHMENTS: As this is the first year of a three year project, the majority of accomplishments to date have been administrative and aimed at a timely and efficient study start-up period.

- DOD IRB: On November 22, 2011, the DoD requested revisions to the protocol and consents were satisfied. After resubmission to the Columbia University Medical Center (CUMC) IRB, approval was granted from the USAMRMC ORP HRPO.

- Columbia University IRB: The CUMC IRB approved version 2.2 of the protocol on January 7, 2011 and the annual renewal was approved on n February 9, 2011.

- Enrollment: Five of the 14 subjects have been enrolled and randomized into the study. Recruitment and enrollment activities continue.

REPORTABLE OUTCOMES: The methods of this study and baseline characteristics of subjects enrolled to date will be presented at the Families of SMA Annual Conference, June 23 – 25, 2011, Orlando Florida (see attached Appendix 2).

CONCLUSION: This report summarizes the first year of a three-year project. In addition to successfully obtaining IRB approvals and completing all relevant study start up procedures, 5 of the 14 planned subjects have been enrolled and randomized. Protocol adherence has been outstanding thus far with only one deviation with regards to visit schedule. All testing and intervention procedures have been well tolerated without any serious adverse events and all non-serious adverse events are closely monitored by an independent safety monitor who has approved continuation of the study without modification thus far. Our original plan was to recruit 14 patients over 9 months. Due to administrative delays, the start date for our enrollment period was pushed back 2 months. As a result our modified enrollment period should come to an end in October 2011. Though we are slightly behind our proposed timeline, we anticipate enrollment to increase during the up-coming summer months.

SO WHAT SECTION: The result of this prospective, single (examiner) blinded, randomized and controlled clinical trial of the effect of exercise on an established functional outcome measure will have immediate impact on clinical practice by providing important guidance to clinical management of SMA patients. The effect of exercise on additional clinical measures as well as on formal exercise performance will provide mechanistic information on the changes underlying any observed improvement in exercise performance. These results would also inform our understanding of the mechanisms underlying weakness and fatigue in SMA.

To our knowledge, this will be the first randomized, controlled clinical trial of exercise in SMA. Even if we do not succeed in establishing the effectiveness of this intervention, this study will establish the safety of exercise in SMA. This study offers an assessment of the potential complications of a comprehensive exercise program in SMA, it will advise and inform future clinical practice by confirming or questioning the current treatment paradigm.

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Columbia SMA Project: A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)

PI: Darryl C. DeVivo, MD

Adverse Event Summary Report By Subject

Reporting period: December 1, 2010 thru April 29, 2011

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
001	Pre-assignment	Pulmo/ Upper Resp	URI / fever	O	Month 1	1/7/2011	12/27/2010	1/12/2011	RC	0	1	No
001	Pre-assignment	Musculo/ Skeletal	Muscle soreness	O	Month 1	1/14/2011	12/18/2010	12/21/2011	RC	2	1	No
001	Pre-assignment	Consti	Fatigue	M	Month 1	1/14/2011	12/18/2010	12/19/2010	RC	2	0	No
001	Pre-assignment	Musculo/ Skeletal	Fall	M	Month 1	1/14/2011	12/20/2010	12/20/2010	RC	0	0	No
001	Pre-assignment	Musculo/ Skeletal	Fall	M	Month 1	1/14/2011	1/6/2011	1/6/2011	RC	0	0	No
001	Pre-assignment	Musculo/ Skeletal	Fall	M	Month 1	1/14/2011	1/8/2011	1/8/2011	RC	0	0	No
001	Pre-assignment	Musculo/ Skeletal	Fall	M	Month 1	1/14/2011	1/10/2011	1/10/2011	RC	0	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	Month 1	1/19/2011	1/19/2011	1/19/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Muscle soreness	O	TC week 5	1/21/2011	1/14/2011	1/17/2011	RC	2	1	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 6	1/28/2011	1/22/2011	1/22/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Low back pain	M	TC week 6	1/28/2011	1/22/2011	2/4/2011	RC	1	2	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 7	2/4/2011	1/28/2011	1/28/2011	RC	1	0	No
001	Exercise	Neurol	Paraesthesias right shoulder	M	TC week 7	2/4/2011	1/31/2011		CO	1	0	No

[1] Grade (M=mild, O=moderate, S=severe, L=life threatening, D=death)

[2] Outcome (RC=Recovered Completely, RR=Recovered Residual Effects, CO=Continuing, UN=Unknown, D= death)

[3] PI Assessment (0= unrelated, 1=possibly related, 2=probably related, 3= definitely related)

[4] Action Taken (0=no action, 1= required medication, 2=other treatment or procedure, 3=discontinuation of exercise, 4= discontinuation from study, 5= other)

Adverse Event Summary Report By Subject

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 7	2/6/2011	2/4/2011	2/17/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 8	2/11/2011	2/7/2011	2/7/2011	RC	1	0	No
001	Exercise	Musculo/ Skeletal	Low back pain	O	TC week 11	3/4/2011	2/24/2011	2/24/2011	RC	1	1	No
001	Exercise	Musculo/ Skeletal	Low back pain	O	TC week 13	3/18/2011	2/26/2011	2/26/2011	RC	1	1	No
001	Exercise	Musculo/ Skeletal	Fall	O	TC week 13	3/18/2011	3/7/2011	3/7/2011	RC	1	1	No
001	Exercise	Musculo/ Skeletal	Fall	M	TC week 15	4/1/2011	4/1/2011	4/1/2011	RC	1	0	No
001	Exercise	Gastro-intestinal	Diarrhea	M	TC week 15	4/1/2011	3/31/2011	4/7/2011	RC	0	0	No
001	Exercise	Musculo/ Skeletal	Low back pain	O	Month 4	4/8/2011	4/6/2011	4/7/2011	RC	1	1	No
001	Exercise	Musculo/ Skeletal	Neck /shoulder pain	M	TC week 18	4/22/2011	4/15/2011		CO	1	0	No
001	Exercise	Musculo/ Skeletal	Low back pain	M	TC week 18	4/22/2011	4/15/2011		CO	1	0	No
002	Pre-assignment	Pulmo/ Upper Resp	Cough / nasal congestion	O	Month 1	2/7/2011	2/3/2011	2/11/2011	RC	0	1	No
002	Pre-assignment	Musculo/ Skeletal	Muscle soreness	O	Month 1	2/7/2011	2/6/2011	2/8/2011	RC	0	1	No

[1] Grade (M=mild, O=moderate, S=severe, L=life threatening, D=death)
[2] Outcome (RC=Recovered Completely, RR=Recovered Residual Effects, CO=Continuing, UN=Unknown, D= death)
[3] PI Assessment (0= unrelated, 1=possibly related, 2=probably related, 3= definitely related)
[4] Action Taken (0=no action, 1= required medication, 2=other treatment or procedure, 3=discontinuation of exercise, 4= discontinuation from study, 5= other)

Adverse Event Summary Report By Subject

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
002	Control	Musculo/ Skeletal	Muscle soreness	O	TC week 7	2/28/2011	2/21/2011	2/22/2011	RC	0	1	No
002	Control	Musculo/ Skeletal	Muscle soreness	O	TC week 7	2/28/2011	2/27/2011	2/28/2011	RC	0	1	No
002	Control	Musculo/ Skeletal	Leg weakness/ fatigue	M	TC week 13	4/25/2011	4/1/2011		CO	0	0	No
002	Control	Musculo/ Skeletal	Fall (1)	M	TC week 13	4/25/2011	4/5/2011	4/5/2011	RC	0	0	No
002	Control	Musculo/ Skeletal	Fall (2)	M	TC week 13	4/25/2011	4/5/2011	4/5/2011	RC	0	0	No
003	Pre-assignment	Neurological	Migraine headache	O	Month 1	3/10/2011	2/14/2011	2/14/2011	RC	0	1	No
003	Pre-assignment	Neurological	Migraine headache	O	Month 1	3/10/2011	3/7/2011	3/7/2011	RC	0	1	No
003	Control	Musculo/ Skeletal	Fall	M	TC week 5	3/15/2011	3/11/2011	3/11/2011	RC	0	0	No
003	Control	Musculo/ Skeletal	Fall	M	TC week 5	3/15/2011	3/13/2011	3/13/2011	RC	0	0	No
003	Control	Neurological	Migraine headache	O	TC week 8	4/5/2011	3/28/2011	3/28/2011	RC	0	1	No
003	Control	Neurological	Migraine headache	O	TC week 8	4/5/2011	4/4/2011	4/4/2011	RC	0	1	No
004	Pre-assignment	Ocular/ Visual	Sty right eye	M	Month 1	4/1/2011	3/25/2011	4/3/2011	RC	0	0	No

[1] Grade (M=mild, O=moderate, S=severe, L=life threatening, D=death)
[2] Outcome (RC=Recovered Completely, RR=Recovered Residual Effects, CO=Continuing, UN=Unknown, D= death)
[3] PI Assessment (0= unrelated, 1=possibly related, 2=probably related, 3= definitely related)
[4] Action Taken (0=no action, 1= required medication, 2=other treatment or procedure, 3=discontinuation of exercise, 4= discontinuation from study, 5= other)

Adverse Event Summary Report By Subject

Subject ID	Treatment Assignment	Category	Description	Grade[1]	Visit	Report Date	Onset Date	Resolution Date	Outcome[2]	PI Assessment[3]	Action Taken[4]	SAE
004	Pre-assignment	Musculo/ Skeletal	Fall (1)	M	Month 1	4/1/2011	3/12/2011	3/12/2011	RC	0	0	No
004	Pre-assignment	Musculo/ Skeletal	Fall (2)	M	Month 1	4/1/2011	3/12/2011	3/12/2011	RC	0	0	No
004	Pre-assignment	Musculo/ Skeletal	Fall	M	Month 1	4/1/2011	3/21/2011	3/21/2011	RC	0	0	No
004	Pre-assignment	Musculo/ Skeletal	Fall	M	Month 1	4/1/2011	3/27/2011	3/27/2011	RC	0	0	No
004	Control	Musculo/ Skeletal	Fall	M	TC week 7	4/20/2011	4/8/2011	4/8/2011	RC	0	0	No
004	Control	Musculo/ Skeletal	Fall	M	TC week 7	4/20/2011	4/15/2011	4/15/2011	RC	0	0	No
004	Control	Musculo/ Skeletal	Fall	M	TC week 7	4/20/2011	4/18/2011	4/18/2011	RC	0	0	No

[1] Grade (M=mild, O=moderate, S=severe, L=life threatening, D=death)
[2] Outcome (RC=Recovered Completely, RR=Recovered Residual Effects, CO=Continuing, UN=Unknown, D= death)
[3] PI Assessment (0= unrelated, 1=possibly related, 2=probably related, 3= definitely related)
[4] Action Taken (0=no action, 1= required medication, 2=other treatment or procedure, 3=discontinuation of exercise, 4= discontinuation from study, 5= other)

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Muscular Dystrophy Association (MDA) Clinic
Spinal Muscular Atrophy Clinical (SMA) Research Center

Nancy E. Strauss, M.D.
Clinical Professor of Rehabilitation Medicine
Diplomate, American Board of Physical Medicine and Rehabilitation
Vice Chair and Residency Program Director in Rehabilitation Medicine

March 7, 2011

Dear Dr. De Vivo:

I am providing the following information concerning the status of Department of Defense Grant; A-15886 "A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)."

I have reviewed, with the study team, the Safety Report submitted on February 28, 2011. This report contained adverse events for subjects 001 and 002 reported from study initiation through and including February 27, 2011.

I am satisfied with the conduct of this study. After carefully reviewing the status of the study, and I conclude that the study should continue without any changes in the conduct of the trial.

Please feel free to contact me directly with questions about this review at 212-305-8592.

Sincerely yours,

Nancy E Strauss MD

Nancy E. Strauss, MD

FAX- JACKIE MONTES 212 305-9263

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Nancy E. Strauss, M.D.
Clinical Professor of Rehabilitation Medicine
Diplomate, American Board of Physical Medicine and Rehabilitation
Vice Chair and Residency Program Director in Rehabilitation Medicine

April 4, 2011

Dear Dr. De Vivo:

I am providing the following information concerning the status of Department of Defense Grant; A-15886 "A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)."

I have reviewed, with the study team, the Safety Report submitted on April 1, 2011. This report contained adverse events for subjects 001, 002 and 003 reported from study initiation through and including March 31, 2011.

I am satisfied with the conduct of this study. After carefully reviewing the status of the study, and I conclude that the study should continue without any changes in the conduct of the trial.

Please feel free to contact me directly with questions about this review at 212-305-8592.

Sincerely yours,

Nancy E. Strauss MD

Nancy E. Strauss, MD

Jackie (VIVO HC) FAX (212) 342-1263

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Clinical Professor of Rehabilitation Medicine
Diplomate, American Board of Physical Medicine and Rehabilitation
Vice Chair and Residency Program Director in Rehabilitation Medicine

May 6, 2011

Dear Dr. De Vivo:

I am providing the following information concerning the status of Department of Defense Grant; A-15886 "A Randomized, Control Trial of the Effects of Exercise on Motor Function and Strength in Patients with Spinal Muscular Atrophy (SMA)."

I have reviewed, with the study team, the Safety Report submitted on May 2, 2011. This report contained adverse events for subjects 001, 002, 003, and 004 reported from study initiation through and including April 29, 2011.

I am satisfied with the conduct of this study. After carefully reviewing the status of the study, and I conclude that the study should continue without any changes in the conduct of the trial.

Please feel free to contact me directly with questions about this review at 212-305-8592.

Sincerely yours,

Nancy E Strauss MD

Nancy E. Strauss, MD

Title: Randomized, Controlled Clinical Trial of Exercise in Patients with Spinal Muscular Atrophy (SMA)

Authors: Jacqueline Montes; Carol Ewing Garber; Megan Montgomery; Shirit Kamil Rosenberg; Sally Dunaway; Douglas Sproule, Darryl C. De Vivo.

Institutions: Columbia University, New York, NY

Background: The potential benefit of exercise has not been addressed with a controlled trial in SMA. Patients with the mild form of SMA, type 3, are an ideal target population for initial studies of exercise because their residual strength makes endurance and strengthening programs feasible.

Objective: The study aims are to assess (1) aerobic exercise combined with a comprehensive strengthening program on clinical measures of function, (2) the effect of a sustained exercise regimen on exercise capacity, and (3) the effect of comprehensive strengthening and aerobic exercise on muscle strength measures in ambulatory SMA patients.

Methods: Fourteen ambulatory participants will be randomly assigned to two cohorts. The experimental group will receive 6 months of intervention, followed by 6 months of closely monitored ongoing treatment designed to maintain evaluator blinding, and 6 months of subject-directed exercise. Group 2 will serve as the control cohort receiving 6 months of exercise intervention starting in the 7^{th} month. The exercise protocol will include a progressive home based cycle ergometry performed five times weekly for 30 minutes, plus a strengthening program performed three times weekly. The primary outcome will be distance walked during the 6 minute walk test (6MWT). Additional clinical and functional measures including gait analysis and exercise capacity.

Results: The research participants will range in age from 8 – 50 years and be able to walk 25 meters unassisted at study entry. We will evaluate the potential benefits of exercise by repeated measures of total distance walked during the 6MWT over a 6 month interval. The secondary analysis will include comparison of mean change over the six month intervention period to mean change over the control period in exercise tolerance (maximal O2 uptake and ventilatory threshold), HFMSE, 10 meter walk/run, quantified physical activity level (as measured using the Actigraph^{TM} uniaxial accelerometer), kinematic gait assessment, FVC, muscle strength, Timed Up and Go test, fatigue, and quality of life. Analysis will follow intent-to-treat principles.

Conclusions: Patients currently are being enrolled. Baseline data and subject characteristics will be presented at the meeting. The results this prospective, single (examiner) blinded, randomized and controlled clinical trial of aerobic and strengthening exercise to improve function in SMA should have an immediate impact on clinical practice by providing important guidelines to management of ambulatory SMA patients.

Acknowledgments: This study is supported by the Department of Defense; USAMRAA Grant/Cooperative award number: 09131005(W81XWH-10-1-0127)